

1 respectfully submits that no new matter has been introduced by this amendment.

2
3 The amendment to the paragraph beginning at page 23, line 28, is to
4 correct the description of the material used to prepare the vessel. Line 30
5 refers to this material as "silastic", which is incorrect, because SILASTIC® is
6 a trademark, for a brand of silicone tubing. Line 26 of p. 23 correctly refers
7 to the use of "silicone" tubing, and therefore, "silastic" in line 30 has been
8 replaced with --silicone-- to describe this material correctly.

9
10 The amendment to the specification at the paragraph beginning at page
11 25, line 17, is to clarify that serum or other substances can be employed where
12 they are under study or required. The use of serum has been described in the
13 specification at p. 25, lines 6-9. One skilled in the art would recognize the
14 use of serum and other substances as described by this amendment.

15
16 The amendment to the specification at p. 27, line 35 is to clarify
17 the properties of the vessel models prepared in Example 1 of the specification
18 (p. 23, line 26 - p. 24, line 29). While the model vessel was chosen for having
19 a structure similar to that of actual human vessels, for the model system to have
20 physiological meaning, one of ordinary skill in the art would realize it is
21 inherent that the model vessel have material properties similar to actual human
22 vessels. Properties of the various types of vessels which could be used are
23 further described in Examples 7 and 8, at p. 27, line 33 - p.29, line 1 of the
24 specification. No new matter has been introduced by this amendment.

25
26 Claims 2, 3, 4 and 6 have been amended.

27
28 Claim 2 has been amended to depend from added claim 11, instead of
29 claim 1. Basis is Figs. 1A, 1B; p. 11, line 35 - p. 17, line 17.

30
31 Claim 3 has been amended to depend from added claim 11, instead of
32 claim 1. Basis is p. 10, line 35 - p. 11, line 7; p. 13, line 28 - p. 14, line
33 8.

34
35 Claims 4 and 6 have been amended to clarify the language of the
36 claim, wherein endothelial cells are the preferable choice for the blood vessel.

1 Basis is Example 2, at p. 24, line 31 - p. 25, line 28 of the specification.

2
3 Please add Claims 7-54, inclusive. These claims are being added to
4 more fully define the invention. Because several of the originally filed claims
5 now depend from the added claims, it was necessary to amend these original
6 claims, and applicant respectfully submits that these amendments are not related
7 to patentability.

8
9 The basis for the added Claims are summarized below:

<u>Claim #(s):</u>	<u>Basis:</u>
7, 33, 37, 38, 49, 51,	Figs. 1A, 1B; P. 15, lines 3-25.
52, 53, 54	
8, 13, 39, 40	P. 16, lines 13-24.
9	Fig. 1A; P. 14, lines 10-19.
10	Figs. 1A, 1C; P. 12, lines 4-16.
11, 23, 24, 25, 26, 27,	Figs. 1A, 1B; P. 11, line 35 - p. 17, line 17.
28, 30, 31, 32	
12	Figs. 1A, 1B; P. 15, lines 18-25.
14	P. 15, lines 18 - 25; p. 16, lines 22-24.
15	P. 15, lines 22-24, lines 31-35.
16	P. 15, lines 22-24.
17	Fig. 1A, 1B; P. 20, lines 3-19.
18, 44	Figs. 1A, 1C; P. 18, line 32 - p. 19, line 4.
19, 45	Figs. 1A, 1C; P. 12, lines 18-27.
20	Figs. 1A, 1C; P. 12, line 29 - p. 13, line 8.
21, 47	Figs. 1C, 1D; P. 18, lines 22-26.
22, 29, 36, 50	P. 23, lines 4-11; p. 23, lines 13-15; p. 23, line 28 - p. 24, line 29; p. 24, line 33 - p. 25, line 15; p. 27, line 35 - p. 28, line 18.
34, 35	Figs. 1A, 1C; P. 20, lines 3-19.
41, 42	P. 16, lines 13-24; p. 16, line 31- p. 17, line 12.
43	Figs. 1A, 1B; P. 12, lines 4-16.
46	Figs. 1A, 1C; Fig. 9; P. 12, line 29 - p. 13, line 8.

2
3 Applicant respectfully submits that these Claims define patentable
4 subject matter, and the Examiner is hereby requested to allow the present Claims.
5

6 In the event that this Amendment does not place the application in
7 condition for allowance, the Examiner is respectfully requested to telephone the
8 undersigned in order that an attempt can be made to place the application in
9 condition for allowance as expeditiously as possible.
10

11 Respectfully submitted,

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31 MPN:BA/s

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: DANCU, MICHAEL et al. Atty. Docket No: 1626-1116
Serial No: 09/973,433 Examiner: (Unknown)
Filed: October 8, 2001 Group Art Unit: (Unknown)

For: SYSTEM AND METHOD TO SIMULATE HEMODYNAMICS

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 14 of page 31 has been amended as follows:

The most common WSS simulating systems utilize a 2-dimensional stiff surface, such as a glass slide, for the endothelial cell culture forming the wall of a parallel plate flow chamber. The WSS in these devices is usually steady because of difficulties in simulating pulsatile flow. Cyclic straining devices provide only strain, by stretching cells on a compliant membrane without flow. Both types of systems are thus limited by their design. However, no studies have been performed studying both parameters (WSS and CS) using cells grown on a single type of support surface because such a

1 system, until now, has remained technologically
2 unfeasible. The present invention addresses and solves
3 this long-felt need by providing a system in which
4 endothelial cells can be grown on a single support
5 surface, and subjected to studies in which both wall
6 shear stress and circumferential strain ~~stress~~ can be
7 examined independently of each other.

8
9 Paragraph beginning at line 18 of page 10 has been amended as
10 follows:

11
12 The present invention is a system for hemodynamic
13 simulation comprising ~~comprises~~ a vessel having
14 properties of a blood vessel, a reservoir containing a
15 quantity of fluid, tubing connecting the vessel and
16 reservoir, and at least one pump for circulating the
17 fluid within the system. Fluid can be tissue culture
18 medium or blood analog fluid, and the vessel may include
19 mammalian cells attached to its inside. A drive system,
20 comprising two reciprocating drive shafts that are
21 coupled by a cam, enables the uncoupling of pulsatile
22 flow and pulsatile pressure to provide independent
23 control over wall shear stress and circumferential
24 strain. The shaft drives two pumps that are 180 degrees
25 out-of-phase and are connected upstream and downstream
26 of the vessel, and effect this uncoupling.

27
28 Paragraph beginning at line 18 of page 15 has been amended as
29 follows:

30
31 Each of pumps 40 and 42 is under the control of a
32 drive system unit 44, which comprises a plurality of
33 independent linear actuators 46. These actuators 46 can
34 be individual, stand alone units, for may be controlled
35 by one or more computer systems 48. In the embodiment
36 in Fig. 1A, the second pumps 40 are connected by a shaft

1 50, and the third pumps 42 are connected by a second
2 shaft 52. In one embodiment of the present invention,
3 in which a 4-bar linkage mechanism is the drive system,
4 a cam 54 affects the control of the various second pumps
5 40 and third pumps 42. In one embodiment of the present
6 invention (Fig. 1B) the drive system unit 44 comprises
7 six computer-controlled linear actuators, while in
8 another embodiment (Fig. 1A) the drive system unit 44
9 comprises four independent computer-controlled linear
10 actuators.
11

12 The paragraph beginning at line 1 of page 14 has been amended as
13 follows:
14

15 A pressure sensor 18 is used for monitoring the
16 internal system pressure, and positioned either upstream
17 and/or downstream of the compliant vessel 12. A
18 pressure sensor can also be placed in the external
19 chamber 36 to monitor external chamber pressure.
20 Pressure sensor 18 can also be a blood pressure catheter
21 (such as, for example, and not intended as a limitation,
22 a MILLAR® catheter (MPC-500 with pressure meter TCB500;
23 Registered Trademark of Millar Instruments Corp.,,
24 Houston TX), in either a fluid contacting or non-
25 contacting version. Pressure sensor 18 may also be a
26 pressure probe, such as those known to those skilled in
27 the art. In one embodiment of the present invention,
28 the pressure sensor is a catheter tip transducer
29 (Millar) which is inserted upstream into the lumen of
30 the compliant vessel. Where cells are being used in the
31 compliant vessel 12, the pressure sensor 18 is kept
32 upstream to avoid damaging the cells. Pressure drop
33 across the compliant vessel has been shown to be
34 negligible.--
35

36 Paragraph beginning at line 28 of page 23 has been amended as

1 follows:

2
3 In this example, the vessel chosen for growth of
4 endothelial cells is a silicone ~~silastic~~ tubing, sold by
5 Dow-Corning, Midland, MI under the brand name of SYLGARD
6 184® elastomer, or Silastic (MDX4-4210), Medical Grade
7 tubing, and used to prepare elastic artery models.
8 These models were prepared using the method described by
9 Lee and Tarbell (1997, and hereby incorporated by
10 reference), and included the preparation of models of
11 human linear and bifurcating arteries.

12
13 The paragraph beginning at line 17, page 25 has been amended as
14 follows:

15
16 Requirements of the fluid 16 include having a
17 viscosity that can be elevated to achieve conditions of
18 physiologic stress at modest flow rates. Dextran is
19 used within the fluid while the present invention uses
20 vessels of approximately 0.79 cm diameter; in instances
21 employing vessels of smaller diameter, addition of
22 dextran is not necessary. The fluid should be free of
23 Phenol Red and serum so as not to interfere with
24 measurements of other cellular products, such as
25 prostacycline or nitric oxide. Serum and other
26 substances can be added to the media if these substances
27 are under study, or if the serum or substance is
28 required by the cell line.

29
30 Paragraph beginning at line 35 of page 27 has been amended as
31 follows:

32
33 Example 1 described the use of vessel models,
34 modeled after the structure and material properties of
35 actual human aortic vessels. In addition to using
36 models of vessels, other vessels can be used in

1 conjunction with the present invention. These can be
2 chosen from the group consisting of an artery, an
3 artificial artery, a vein, human umbilical tissue, or a
4 non-rigid tube. The artery may comprise a bovine aorta,
5 or a human coronary artery. The vein may comprise
6 bovine veins, or human veins such as a human leg vein or
7 a human umbilical vein. Bovine tissue can be obtained
8 from commercial supply sources, such as Vec
9 Technologies, Ithaca NY and human umbilical materials
10 can be obtained a local hospital, or a commercial
11 sources such as Clonetics, Vec Technologies, or other
12 sources known to those skilled in the art. In addition
13 to studying the effects of hemodynamic conditions on
14 endothelial cells, other types of cells can also be
15 used, including smooth muscle cells, cartilage cells,
16 osteocytes, embryonic and adult stem cells, and the
17 like.

18
19 In the Claims:

20
21 2. (Amended) The system as described in claim 11~~1~~, wherein the
22 vessel preferably is a model of a mammalian blood vessel.

23
24 3. (Amended) The system as described in claim 11~~2~~, wherein the
25 vessel is biocompatible.

26
27 4. (Amended) The system as described in claim 2, wherein the vessel
28 more preferably ~~further~~ comprises endothelial cells from a mammal.

29
30 6. (Amended) The method as described in claim 5, wherein the vessel
31 more preferably ~~further~~ comprises endothelial cells from a mammal.

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